REMARKS

Claim 57 is canceled without prejudice or disclaimer. Claims 56, 59 and 61-63 are amended. Claims 64-65 are added. The amended claims are supported throughout the specification as filed, including p. 9, lines 18-19 ("wherein said positions correspond to the amino acid positions of SEQ ID NO:1") and p. 25, line 33 to p. 27, line 16 ("mobile or highly mobile region") of the substitute specification, as well as the previously pending claims.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

Applicants acknowledge with appreciation the Examiner's acceptance of the substitute specification and amended sequence listing filed April 16, 2007.

I. Objections to the Claims

Claim 63 is objected to under 37 CFR 1.75(c) as being of improper dependent form. Applicants have amended claim 63 to depend from claim 62, thus obviating the objection.

Claim 57 is objected to for reciting "are selected." Applicants have amended claim 57 to recite the singular form of the verb, thus obviating the objection.

Claim 61 is objected to for having a non-sequential ordering of the positions for substitution and for repeating an alternative substitution. Applicants have amended the claim to sequentially order the positions for substitution and to include a dependent claim directed to the modification H200D+D196N or H200N+D196N, thus obviating the objection.

II. The Rejection of Claims 56-57 and 59-63 under 35 U.S.C. 112 (Written Description)

Claims 56-57 and 59-63 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. This rejection is respectfully traversed.

First, to the extent that the rejection is directed to the use of the terms "similarity", "variant" and/or "JP170 type subtilase" in the claims, applicants point out that these terms are clearly set forth in the specification as filed. See, e.g., p. 8, lines 7-24 ("similarity"); p. 7, lines 31-33; and p. 11, lines 5-13 ("JP170 type subtilase") of the substitute specification.

Moreover, the written description requirement of the Patent Code is fulfilled when the patent specification describes the claimed invention in sufficient detail such that one skilled in the art can

reasonably conclude that the inventor had possession of the claimed invention. See *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The written description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

While applicants disagree with the Examiner's contentions, applicants respectfully submit that this rejection is rendered moot by the amended claims, which recite a similarity of at least 95% to SEQ ID NO:1. Applicants respectfully submit that the claimed subject matter is described in the specification in a manner that reasonably conveys to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, an artisan would appreciate that applicants had possession of variants which are 95% similar to the reference sequence, SEQ ID NO:1. The specification fully describes the variants of the present disclosure. Applicants therefore submit that the specification demonstrates that applicants had possession of the claimed invention at the time the application was filed.

For the foregoing reasons, Applicants submit that the amended claims overcome this rejection under 35 U.S.C. 112, first paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 56-57 and 59 under 35 U.S.C. 112 (Enablement)

Claims 56-57 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of a variant JP170 subtilase wherein the variant subtilase has an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:1 allegedly does not reasonably provide enablement for the preparation and use of a variant subtilase having 43 or more amino acid sequence modifications in the amino acid sequence of SEQ ID NO:1.[1] This rejection is respectfully traversed.

While applicants disagree with the Examiner's contentions, solely to expedite prosecution, applicants have amended the claims to recite a similarity of at least 95% to SEQ ID NO:1, thus rendering the rejection moot.

For the foregoing reasons, Applicants submit that the amended claims overcome this rejection under 35 U.S.C. 112, first paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection.

[1] Applicants respectfully submit that the Examiner's reference to "SEQ ID NO:2" at page 4 of the rejection is in error and that reference to "SEQ ID NO:1" was intended.

IV. The Rejection of Claims 56-57 and 59-63 under 35 U.S.C. 112, Second Paragraph

Claims 56-57 and 59-63 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. This rejection is respectfully traversed.

With respect to the alleged failure of claims 56-57 and 60-62 to state any fixed point or coordinate for measuring the "modification in an amino acid residue in a position located at a distance of 10Å (6Å) or less to," applicants respectfully submit that many of the Examiner's objections have been obviated by the amendments herewith. Moreover, applicants submit that the specification as filed clearly sets forth the identification and position of the ion binding sites of the claimed JP170 type subtilase variants, based on applicants' knowledge of the three-dimensional structure of the subtilase and its homologues. See, e.g., p. 15, line 15 to p. 18, line 9 of the substitute specification. Thus, the metes and bounds of those positions which are within 10Å (6Å) of the metal ion of the ion binding site are readily ascertainable to those of skill in the art based on applicants' disclosure. See, e.g., p. 18, lines 1-9 of the substitute specification. Applicants also disagree with the Examiner's characterization of claim 62 as directed to "presumably a 'weak' site" and point out that claim 62 is directed to the introduction to a variant of a JP170 type subtilase of an ion-binding site corresponding to the Strong ion-binding site of the BPN' like family subtilases.

Claim 63 stands rejected as indefinite for stating the terms "optionally ... and/or." Applicants have amended claim 63 to delete this language, and have added claim 65, thus obviating this rejection.

The Examiner contends that claims 57, 59 and 61-63 are indefinite for failing to require that particular, or intended, positions be modified. Applicants have amended claims 56 (now incorporating the limitations of former claim 57), 59 and 62 to recite "wherein said positions correspond to the amino acid positions of SEQ ID NO:1" as suggested by the Examiner, thus obviating this rejection.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. The Rejection of Claims 56-57 and 59-61 under 35 U.S.C. 102

Claims 56-57 and 59-61 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Hatada et al., EP 1 209 233 (hereinafter, "Hatada EP '233") and under 35 U.S.C. 102(e) as allegedly being anticipated by Hatada et al., US 6,803,222 (hereinafter "Hatada US '222"). The

Examiner states that the amino acid sequence of the alkaline protease of SEQ ID NO:1 of Hatada EP '233 is identical to SEQ ID NO:1 of the instant application. The Examiner states that Hatada EP '233 anticipates claims 56-57 and 59-61 and pages 2-4 of Hatada EP '233 disclose amino acids at positions 193, 195, 342 and 369 replaced with a different amino acid. The Examiner also states that the amino acid sequence of the alkaline protease of SEQ ID NO:1 of Hatada US '222 is identical to SEQ ID NO:1 of the instant application. The Examiner states that Hatada US '222 anticipates claims 56-57 and 59-61 and col. 1-7 and Figures 1-3 of Hatada US '222 disclose amino acids at positions 193, 195, 342 and 369 replaced with a different amino acid. This rejection is respectfully traversed.

In order to expedite prosecution, applicants have amended the claims to delete reference to certain amino acid positions, and respectfully submit that the amendment obviates the rejection.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. The Rejection of Claim 39 under 35 U.S.C. 103

Claim 39 is rejected under 35 U.S.C. 103 as allegedly being unpatentable over Sloma et al., US 5,891,701 (hereinafter, "Sloma") in view of Zukowski et al., US 5,397,705 (hereinafter, "Zukowski"). The Examiner states that, regardless of whether or not a three-dimensional structure of the JP170 subtilase is determined after it has been crystallized, Sloma teach that amino acid substitutions should be made in the JP170 subtilase for the same kinds of reasons, well-known in the prior art, that amino acid substitutions were made in other subtilases, e.g., modifying the thermostability, oxidative stability, specific activity and pH optimum. The Examiner further states that the skilled artisan would have considered Zukowski, which goes beyond teaching certain positions within a calcium ion binding site that may be modified to reinforce calcium binding to produce increased thermal stability of another subtilase. The Examiner cites Hatada EP '222 as evidence that resolution of the three-dimensional structure of JP170 protease was unnecessary to a determination of where to make worthwhile, stabilizing modifications. The Examiner further states that Zukowski teach that stability of any subtilase is improved by substituting for either asparagine or glycine within an asparagine-lysine pair; or by substituting alanine or leucine for methionine. This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference

teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 59, as amended, relates to a variant of a JP170 type subtilase comprising at least one modification in a mobile or highly mobile region wherein the modification is in one or more of the claim-designated amino acid positions of SEQ ID NO:1, wherein the subtilase has at least 95% identity to SEQ ID NO:1.

Sloma relates to isolated nucleic acid sequences encoding polypeptides having protease activity, in which the polypeptides are obtainable from an alkalophilic Bacillus species having enhanced stability towards bleaching agents of the peroxy type. Although Sloma teaches the amino acid sequence of SEQ ID NO:1 of applicants' disclosure, the Examiner has correctly asserted previously that Sloma does not teach any particular regions within the amino acid sequence of the JP170 subtilase for the substitution of amino acids.

Zukowski and Hatada EP '222 also fail to cure the deficiencies of Sloma. In particular, nowhere does Zukowski and/or Hatada EP '222 describe a variant of JP170 type subtilase including at least one modification in a mobile or highly mobile region wherein the modification is in one or more of the claim-designated amino acid positions of SEQ ID NO:1, wherein the subtilase has at least 95% similarity to SEQ ID NO:1. Thus, nowhere do Sloma, Zukowski or Hatada EP '222, either alone or in combination, teach or suggest a variant of JP170 type subtilase including at least one modification in a mobile or highly mobile region wherein the modification is in one or more of the claim-designated amino acid positions of SEQ ID NO:1, wherein the subtilase has at least 95% similarity to SEQ ID NO:1.

Moreover, amended claim 59 recites that the modifications therein are within a mobile or highly mobile region of the JP170 type subtilase. See, e.g., p. 25, line 33 to p. 27, line 16 of the substitute specification. Accordingly, claim 59 clearly reflects applicants' knowledge of the three-dimensional structure of a subtilase, or a close homologue thereof, rather than a mere generalized modification, which is, at best, all that is suggested by the cited references.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. The Examiner's Conclusion

Applicants acknowledge with appreciation the Examiner's statement that claims 62-63 are free of prior art of record.

The Examiner also made of record Svendsen et al., US 7,294,499 (hereinafter, "Svendsen") but did not rely on any of these references as a basis for rejecting the claims of the present application. For this reason, applicants do not address Svendsen herein but note that Svendsen does not render the present claims unpatentable.

VIII. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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